National Institute of Dental and Craniofacial Research

National Advisory Dental and Craniofacial Research Council

Minutes of Meeting
January 23, 2019

Building 45
Conference Room E1/E2
National Institutes of Health
Bethesda, Maryland

U.S. DEPARTMENT OF HEALTH
AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

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NATIONAL INSTITUTE OF DENTAL AND CRANIOFACIAL RESEARCH

MINUTES OF THE

NATIONAL ADVISORY DENTAL AND CRANIOFACIAL RESEARCH COUNCIL

January 23, 2019

The 220th meeting of the National Advisory Dental and Craniofacial Research Council (NADCRC) was convened on January 23, 2019, at 8:30 a.m., in Building 45, Conference Rooms E1/E2, National Institutes of Health (NIH), Bethesda, Maryland. The meeting was open to the public from 8:30 a.m. until 11:43 a.m.; it was followed by the closed session for Council business and consideration of grant applications from 1:00 p.m. until adjournment at 2:20 p.m. Dr. Martha Somerman presided as Chair.

OPEN SESSION

Members Present

Dr. Kathryn Marie Albers
Dr. Shenda M. Baker
Dr. David J. Couper
Dr. Nisha J. D'Silva
Dr. Daniel Malamud
Dr. Daniel W. McNeil (via telephone)
Dr. Sanjay Shete
Dr. Clark M. Stanford (via telephone)
Dr. Joel L. Strom (via telephone)

Ad Hoc Members

Dr. Raul Garcia
Dr. Lee Niswander
Dr. Wenyuan Shi

Members of the Public

Ryne Chua, Program Manager for Advocacy and Governmental Relations, American Dental Education Association (ADEA), Washington, D.C.
Dr. Christopher Fox, Executive Director, IADR/AADR, Alexandria, VA.
Mr. Adam Hockaday, Duke University, Durham, North Carolina.

Dr. Joel Islam, Scientist and Head of Food Microbiology Laboratory, Laboratory for Enteric Microbiology, International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka, Bangladesh.

Dr. Michael Longaker, Deane P. and Louise Mitchell Professor, Vice Chair, Department of Surgery, Co-Director, Institute for Stem Cell Biology and Regenerative Medicine, and Director, Hagey Laboratory for Pediatric Regenerative Medicine, Stanford University, Stanford, California.

Ms. Toni Reeves, Together Educating People (TEP) Services, Washington, D.C.

Ms. Christina Thomas, Director for Government Affairs, American Dental Education Association (ADEA), Washington, D.C.

National Institute of Dental and Craniofacial Research

Dr. Martha J. Somerman, Director
Dr. Douglas M. Sheeley, Deputy Director
Dr. Alicia Dombroski, Executive Secretary, and Director, Division of Extramural Activities (DEA)
Dr. Lillian Shum, Director, Division of Extramural Research (DER)
Dr. Matthew P. Hoffman, Scientific Director, Division of Intramural Research (DIR)
Dr. Marian Young, Deputy Director, DIR, Molecular Biology of Bones & Teeth Section (MBBTS)
Dr. Janice Lee, DIR, Craniofacial Anomalies & Regeneration Section (CARS)
Ms. Karina Boehm, Office of the Director (OD), Office of Communications and Health Education (OCHE)
Dr. Latarsha Carithers, DEA, Scientific Review Branch (SRB)
Dr. Preethi Chander, DER, Integrative Biology and Infectious Diseases Branch (IBIDB)
Mr. Jamil Cherry, DIR
Ms. Jennifer Chi, OD, Office of Clinical Trials Operation and Management (OCTOM)
Ms. Vicki Contie, OD, OCHE, Science Communication and Digital Outreach Branch (SCDOB)
Ms. Mary Cutting, DER, Center for Clinical Research (CCR)
Mr. Bret Dean, OD, Office of Administrative Management (OAM), Financial Management Branch (FMB)
Dr. Olga Epifano, DEA
Ms. Catherine Evans, OD, OCHE
Dr. Dena Fischer, DER, CCR
Dr. Leslie Frieden, DEA, Research Training and Career Development Branch (RTCDB)
Dr. Crina Frincu, DEA, SRB
Dr. Gallya Gannot, DER, CCR
Dr. Nicole Garcia-Quijano, OD, OCHE
Mr. Joel Guzman, DER
Ms. Jeannine Helm, DER
Mr. Gabriel Hidalgo, DEA, Grants Management Branch (GMB)
Dr. Lynn King, DEA, RTCDB
Dr. Wendy Knosp, OD, OSPA
Dr. Orlando Lopez, DER, IBIDB

Ms. Susan Medve, DEA, GMB
Dr. Nadya Lumelsky, DER, IBIDB
Dr. R. Dwayne Lunsford, DER, IBIDB
Ms. Jayne Lura-Brown, DER
Dr. Yun Mei, DEA, SRB
Ms. Yasamin Moghadam, DER, CCR
Dr. Morgan O'Hayre, OD
Mr. Joshua Peoples, DEA, GMB
Ms. Debbie Pettitt, DEA, GMB
Dr. Deborah Philp, DIR, Office of Intramural Training
Dr. Melissa Riddle, DER, Behavioral and Social Science Research Branch (BSSRB)
Dr. Pamela Robey, DIR, Skeletal Biology Section (SBS)
Ms. Delores Robinson, DEA
Ms. Diana Rutberg, DEA, GMB
Dr. Reut Shainer, DIR, MBBTS
Dr. Yasaman Shirazi, DEA, SRB
Mr. Larry Sutton, OD, OAM
Dr. Joseph Tiano, OD, OSPA
Dr. Yolanda Vallejo, DER, IBIDB
Dr. Jason Wan, DER, IBIDB
Dr. S. Chiayeng Wang, DER, IBIDB
Dr. Darien Weatherspoon, DER, CCR
Dr. Achim Werner, DIR, Stem Cell Biochemistry Unit
Ms. Madison Zamora, Post Baccalaureate IRTA Fellow, DIR
Dr. Gary Zhang, DEA, SRB

Other Federal Employees

Dr. David Moss, Senior Dental Public Health Staff Officer, Office of the Surgeon General, US Army, Falls Church, VA.

Ms. Melinda Nelson, Acting Director, Division of Extramural Research Activities (DERA), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institutes of Health, Bethesda, MD.

Dr. Amy Patterson, Chief Science Advisor, Director, Scientific Research Programs, Policy, and Strategic Initiatives, Immediate Office of the Director (IOD), National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, Bethesda, MD.

I. WELCOME AND INTRODUCTIONS

Dr. Martha Somerman, Director, NIDCR, called the open session of the 220th meeting of the Council to order. She welcomed everyone and thanked Council members and others present for their work and participation. She asked guests to introduce themselves.

Dr. Alicia Dombroski, Executive Secretary, NADCRC, and Director, Division of Extramural Activities (DEA), additionally welcomed Drs. McNeil, Stanford, and Strom, who were participating by telephone, those participating via the NIH videocast (http://videocast.nih.gov), and Dr. Lee Niswander, a pending Council member.

II. APPROVAL OF MINUTES FROM PREVIOUS MEETING

Dr. Dombroski invited the Council to consider and approve the minutes of the September 13, 2018, Council meeting. The Council unanimously approved the minutes.

III. ANNUAL REVIEW OF COUNCIL OPERATING PROCEDURES

Dr. Dombroski led the annual review of the Council's operating procedures. Dr. Dombroski invited to Council to suggest changes, make comments, or raise questions on the "Operating Procedures of the National Advisory Dental and Craniofacial Research Council".

The Council unanimously approved the operating procedures.

IV. REPORT OF THE DIRECTOR, NIDCR

Dr. Somerman began her presentation by reflecting on 2018, which was a strong year for research. She expressed her appreciation for the support of NIH leadership, including Dr. Francis Collins, Director of the NIH, and Dr. Lawrence Tabak, Principal Deputy Director of the NIH. She remembered Dr. Stephen Katz, Director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), who passed away in December 2018. He was a key leader at NIH, and she expressed gratitude for his leadership, warmth, and passion.

Dr. Somerman introduced several new NIDCR staff members. For the Division of Extramural Research (DER), she introduced Dr. Emir Khatipov, Director of the Data Science, Computational Biology and Informatics Program, and Dr. Elise Rice, Program Officer in the Behavioral and Social Science Program. For the Division of Intramural Research (DIR), she introduced Dr. Marian Young, Deputy Scientific Director, and Dr. Laura Kerosuo, Stadtman Tenure-Track Investigator. For the NIDCR Dental Clinic, she introduced Dr. Marie Y. Kao, NIDCR Hospital Dentist and Chief of Dental Clinic Operations. For the Office of Clinical Trials Operations and Management, she introduced Jennifer Chi, Clinical Research Manager.

The percentage of clinicians and scientists serving in the 118th Congress has increased to 7% of the House of Representatives and 3% of the Senate. New members make up 20% of the 118th Congress, making it especially important for the Council and those in the field to participate in educating the new members of Congress about NIDCR and NIH. Women make up 24% of the House and 24% of the Senate, and veterans make up 18% of the House and 18% of the Senate. There are now five dentists in the House, with the most recent being Dr. Jeff Van Drew from New Jersey. NIDCR is excited to work with and get to know Dr. Van Drew. Other NIDCR supporters include Representative Elijah Cummings and Representative GK Butterfield.

NIH and NIDCR will see an increase in FY 2019 appropriations. It is expected to be a roughly 5.4% increase for NIH and a 3.4% increase for NIDCR. The NIH has several targeted projects relating to the 21st Century Cures Act. Due to bipartisan support from Congress and NIH

leadership, NIDCR has seen an increase in appropriations over the past several years, for which it is grateful. Dr. Somerman thanked advocates and others for their support.

Dr. Somerman broke down the FY 2018 budget. About 79% went to extramural research and 15% to intramural research. Forty percent of the intramural budget covered central assessments, while 6% went to research management and support (RMS). The majority of the intramural budget goes towards research projects grants (RPGs). The distribution of RPGs has not changed significantly over the past few years. NIDCR's success rate was 22.2% in FY2018, which is aligned with NIH's success rate. Dr. Somerman thanked the Council for the concepts they approved at previous Council meetings in 2018. NIDCR is very actively involved in the NIH-wide efforts in prevention of opioid misuse and abuse and is eager for proposals.

NIH has two new Institute directors: Helene Langevin, Director of the National Center for Complementary and Integrative Health (NCCIH), and Bruce Tromberg, Director of the National Institute of Biomedical Imaging and Bioengineering (NIBIB). The Advisory Committee to the NIH Director (ACD) will be meeting in June. The ACD is focusing on several topics, including artificial intelligence and the Helping to End Addiction Long-Term (HEAL) initiatives. Dr. Somerman encouraged Council members to watch the meeting or webcast.

In 2017, NIDCR launched the NIDCR 2030: Envisioning the Future, Together concept at the American Association of Dental Research. This concept is a major focus for NIDCR, and states that, in 2030, NICDR imagines a world in which

- Dental, oral and craniofacial health and disease are understood in the context of the whole body
- Research informs the strategies used to promote health, prevent and treat disease, and overcome disparities in health
- All people have the opportunity to lead healthy lives

NIDCR's current strategic plan ends in 2019, and NIDCR 2030 will help guide the 2020 strategic plan.

Dr. Somerman is proud of the first Intramural Director's Postdoctoral Fellowship to Enhance Diversity in Dental, Oral, and Craniofacial Research, which was awarded in October 2018. NIDCR hopes to make additional awards in 2019. On May 6th, NIDCR will be celebrating 70 years. Council members should stay tuned for upcoming workshops and symposiums on rare diseases and dental fear and anxiety.

Dr. Somerman presented research highlights from NIDCR's intramural and extramural research programs. The intramural highlight was spearheaded by Dr. Larry Fisher. He and his colleagues identified extracellular matrix molecules, small integrin-binding ligand N-linked glycoproteins (SIBLINGs), which are found in high concentrations in bones and teeth. They found that one of the SIBLINGs, dentin sialophosphoprotein (DSPP), when mutated can cause a type of dentinogenesis imperfecta. They found that DSPP uses a specific tripeptide region for normal secretion, and that mutated DSPP does not transport properly. They identified Surf4, a protein that is critical to transport DSPP from the endoplasmic reticulum (ER). If DSPP is not transported, damaging protein aggregates form inside the ER. This research sets the groundwork for potential targeted therapy for dentinogenesis imperfecta.

Highlighting extramural achievements, a group of researchers identified that Smad7 has preventative and therapeutic effects on oral mucositis in mouse models without hindering the effectiveness of oral cancer radiation therapy. This is an important topic because oral mucositis is often a severe side effect of radiation and chemotherapy. The researchers are now exploring topical application of Smad7 to oral mucositis lesions to prevent a systemic impact. They tested this by delivering Smad7 to tumor-bearing mice through a Tat-Smad7. The Smad7 promoted healing of the oral mucositis but did not affect the cancer treatment or cause a proliferation of the cancer cells. The researchers will continue clinical studies in this area.

Dr. Somerman discussed activities occurring in the regenerative medicine field. A few years ago, the National Academy of Medicine (NAM) launched its Regenerative Medicine Forum, of which NIDCR was a co-chair and is now the lead for NIH. The Dental, Oral, and Craniofacial Tissue Regeneration Consortium (DOCTRC) is in phase 2 of the NIDCR Regenerative Medicine Initiative. In terms of percentage of Institute funding, NIDCR has the second highest for regenerative medicine and the third highest for stem cell research at NIH.

Dr. Somerman asked Council members and meeting participants to stay engaged in upcoming activities, including NIDCR's craniofacial research symposium on May 6, the development of the 2020 Surgeon General's Report on Oral Health, and the launch of NAM's temporomandibular disorders (TMD) consensus study.

V. TRIENNIAL REPORT ON NIH INCLUSION GUIDELINES

Dr. Dena Fischer, Acting Director, Center for Clinical Research, presented the triennial report on NIDCR's compliance with NIH inclusion guidelines. The NIH Revitalization Act of 1993 required that NIH establish guidelines for the inclusion of women and minorities in NIH-funded clinical research. The 21st Century Cures Act instituted a number of requirements for inclusion, including a requirement for Phase III clinical trials to report results of analyses by sex/gender and/or race/ethnicity to www.ClinicalTrials.gov, and a requirement to consider individuals of all ages in NIH-funded clinical research and to report participant age at enrollment in annual progress reports. The policy resulting from the age inclusion requirement will come into effect for grant applications with due dates on or after January 25th, 2019. The 21st Century Cures Act also revised the frequency on reporting adherence to inclusion guidelines from a biennial to a triennial requirement. This is the first triennial report and will include information about fiscal years (FY) 2016, 2017, and 2018. The last biennial report to Council was in May 2018 and reported inclusion information about FY2015 and FY2016.

The inclusion data for this report were obtained from awardee institutions, reported through annual progress reports into the NIH's the Human Subject System. In FY2016, over 65,000 subjects were enrolled in 119 NIDCR-funded intramural and extramural clinical studies. In FY2017, over 56,000 subjects were enrolled in 129 studies, and in FY2018, over 68,000 subjects were enrolled in 152 studies. Female enrollment remained relatively constant across the three years at slightly greater than 50%. Hispanic or Latino ethnicity enrollment also remained relatively constant and ranged from 12.1% to 13.8%. Unknown/not reported ethnicity enrollment ranged from 3.7% to 5% across the three years. The majority of

participants self-reported their race as white, with the percentage ranging from 62.7% to 68% across the three-year reporting timeframe. Black/African American enrollment ranged from 8.8% to 15.6%, and Asian enrollment stayed relatively constant, ranging from 9.1% to 11.6%. Unknown/not reported race enrollment ranged from 5.4% to 8.4% across the three years.

In FY2016, 1,634 subjects were enrolled in five NIDCR-funded intramural and extramural Phase III trials. In FY2017, 1,548 subjects were enrolled in four trials, and in FY2018, 1,627 subjects were enrolled in five trials. Female enrollment was greater in Phase III clinical trials, ranging from 60.2% to 67.3% across the three-year reporting timeframe. Hispanic or Latino ethnicity enrollment remained similar to that of the overall NIDCR-funded clinical research, ranging from 10.1% to 14%. In all three years, at least one third of Phase III participants self-reported as unknown or not reported ethnicity. Phase III trial enrollment by race remained relatively constant for FY2016 and FY2017, with changes in FY2018. In FY2016 and FY2017, about 65% of participants self-reported as white, and in FY2018 this number decreased to 51.2%. Black/African American enrollment ranged from 18.6% to 22.5% and in FY18 increased to 33.1%. Unknown/not reported race enrollment remained similar to that of the overall NIDCR-funded clinical research, ranging from 5.4% to 9.6% across the three years.

The Council unanimously approved the triennial report on NIDCR's compliance with NIH inclusion guidelines.

VI. SPECIAL SESSION ON STEM CELLS AND REGENERATIVE MEDICINE

Overview of Regenerative Medicine Program: from Basic Research to Clinical Applications

Dr. Nadya Lumelsky, Director, Tissue Engineering and Regenerative Medicine Program; Chief, Integrative Biology and Infectious Diseases Branch, led the discussion. The main purpose of the Regenerative Medicine Program is to promote the healing, regeneration, and reconstruction of dental, oral, and craniofacial (DOC) tissues. NIDCR was one of the first institutes at NIH to invest in the field of regenerative medicine and tissue engineering and continues to support this field. Funding for regenerative medicine has been steady, with increases in the last two years, primarily due to the establishment of the Dental, Oral and Craniofacial Tissue Regeneration Consortium (DOCTRC). A large percentage of NIDCR's regenerative medicine budget is used for basic research. About one third of this budget is used for translational research, and a small amount for clinical research. NIDCR is determined to move regenerative medicine research into the clinical domain in the future. Supported research includes mechanistic studies of DOC tissue development, design of novel biomaterials and scaffolds for tissue regeneration, exploration of the nature and mechanisms of action of DOC stem and progenitor cells, wound healing and inflammation resolution, and mechanistic studies of tissue regeneration. The Program also supports translational areas such as *in vivo* drug and molecule delivery, use of bioreactors to generate DOC tissue constructs, use of 3D bioprinting technologies to develop tissue chips, development of DOC-specific animal

models, functional integration of tissue constructs into the host, development scaling up, validation quality control methodologies.

Two areas of high emphasis in the program are autotherapies and the DOCTRC. Autotherapies are minimally-invasive approaches to allow precise manipulation of the endogenous tissue microenvironment for enhancing tissue healing and regeneration. Over the last several years, more tools have become available to allow for endogenous manipulation of tissue microenvironment. Dr. Lumelsky and other NIDCR staff recently published an opinion piece in *Trends in Molecular Medicine* that discussed autotherapies' potential for tissue regeneration. The three major tenets of autotherapy are normalizing the stem-cell niche, promoting a proregenerative environment, and enabling lineage reprogramming. Chronic inflammation creates a "hostile" microenvironment for tissue regeneration, which can be converted into a proregenerative microenvironment by resolving chronic inflammation. However, certain types of inflammatory responses are important for tissue regeneration, and therefore it is important to have precise modulation of the inflammatory microenvironment. Also, it will also be important to enable direct lineage reprogramming *in vivo* of one cell type to another to generate cell sources for tissue regeneration. For example, generation of ameloblasts, which are not available in adult humans, from other cell types, would be very useful. A wide range of tools is available to support these tenets, including biomaterials that provide cell homing cues and respond to changes in the microenvironment.

NIDCR strives to bring this research in regenerative medicine from the basic to the clinical realm but recognizes that this transition is associated with many challenges. To address these challenges, NIDCR established the DOCTRC. The goal of the DOCTRC is to develop effective clinically-relevant strategies for healing and regeneration of tissues of the human DOC complex and make them ready for initiation of Phase 1 clinical trials. The DOCTRC is a multidisciplinary effort that includes clinicians, bioengineers, basic scientists, regulatory, industry, and intellectual property experts, among others. The DOCTRC constitutes a significant portion of NIDCR's regenerative medicine budget. These expenses are justified because the costs increase significantly as technologies move along the translational pipeline. NIDCR expects that the DOCTRC will serve as a general paradigm for translation of regenerative medicine technologies to the clinic for a broad range of tissues in the human body.

Based on the recommendations of clinicians, the DOCTRC developed a list of the most promising individual projects to pursue. The technologies being developed by these projects will undergo pre-clinical testing, with the goal of submitting Investigational New Drug (IND) or Investigational Device Exemption (IDE) applications to the FDA to initiate clinical trials. DOCTRC grants will not support clinical trials themselves but those studies can be supported by other NIDCR mechanisms. The DOCTRC's timeline has three stages. For Stage 1, NIDCR awarded ten groups to prepare Stage 2 applications. For Stage 2, NIDCR awarded two Resource Center (RCs) to deliver administrative, scientific and regulatory support to the Interdisciplinary Translational Projects (ITPs), which are developing a specific tissue engineering or regenerative medicine approach for a functional DOC tissue that synergizes with the expertise of the RC. In Stage 3 the number of ITPs will be reduced, with

only the ones with the highest translational potential being retained. NIDCR expects that in the near future it will be able to hold a special Council session on the DOCTRC's achievements.

Regenerative Medicine Innovation Project

Dr. Amy Patterson, Chief Science Advisor and Director of Scientific Research Programs, Policy, and Strategic Initiatives at the National Heart Lung and Blood Institute, presented on the NIH Regenerative Medicine Innovation Project (RMIP) which is part of the Congressionally-mandated 21st Century Cures Act. Inclusion of regenerative medicine in the Act is a testament to the field's importance to the Congress. Although there have been significant advances made in the regenerative medicine field, there has also been a lot of marketing hype around unproven and untested regenerative medicine products to patients, with sometimes tragic results. These tragic results not only impact patients, they erode public trust in regenerative medicine and biomedical research.

The Act's provisions regarding regenerative medicine are applicable to NIH, the Food and Drug Administration (FDA), and the National Institute of Standards and Technology (NIST). The provisions aim to accelerate progress towards safe and effective therapies that are supported by scientific evidence and rigor and are subject to clear regulatory oversight. Many of the provisions encourage engagement with the private sector. The Act has a provision requiring that awardee institutions match every federally-awarded dollar with at least one non-federal dollar. The Act directs "the NIH, in coordination with the FDA, to award grants and contracts for clinical research to further the field of regenerative medicine using adult stem cells, including autologous stem cells." NIH has decided to interpret the term "adult stem cells" broadly, to include lineage-committed stem cells, induced pluripotent stem cells, and mesenchymal stem cells.

NIH has created a trans-NIH subject matter expert group and a trans-NIH senior oversight committee that reports to the NIH Director and the Advisory Committee to the Director (ACD). NIH has engaged with the FDA, NIST and the Department of Defense (DOD) in a variety of RMIP-related activities. For the first year of RMPIP funding, FY2017, NIH issued a Funding Opportunity Announcement (FOA) to support supplemental (competing revision) awards to existing NIH grants in regenerative medicine from several Institutes and Centers (ICs). Following peer review, NIH funded eight outstanding, highly-meritorious grants. These are all late-transitional projects and they encompass an impressive variety of clinical indications.

To further develop the RMIP plan of action, the RMIP leadership reached out to the NIH community, federal partners, the ACD, and the research community for comments on the critical gaps and challenges in the field of regenerative medicine. The community recognized several critical challenges in translational regenerative medicine: manufacturing of clinical grade products, regulatory assistance and coaching, and a growing but still limited understanding of the in-depth biological properties of stem cells, both *ex vivo* and *in vivo*. It has also been widely-recognized by the surveyed community that difficulties in clinical-grade manufacturing are related both to the intrinsic nature of cell-based products and the difficulty

that academic researchers encounter in obtaining affordable support in different aspects of the clinical translation process.

The funding authorized for FY2018 and beyond, including non-federal matching contributions, is at least $56 million. NIH has a two-fold RMIP strategy. First, NIH plans to solicit and fund late-stage pre-clinical IND- and IDE-enabling studies and strong evidence-based clinical trials that have a potential to significantly accelerate the field of regenerative medicine. Toward this end, in August 2018, NIH published four RMIP FOAs, all of which are cooperative agreement solicitations. Second, NIH plans to facilitate clinical research by providing resources to address the three challenges described above. Specifically, NIH is establishing the Regenerative Medicine Innovation Catalyst (RMIC), which plans to bring together a collaborative network of individual entities and institutions to provide regulatory support, manufacturing assistance, in-depth cell characterization, and secondary analysis of data and clinical outcomes from clinical trials.

NIH intends to support in-depth cell characterization studies and to couple the data obtained from these studies with clinical outcomes in order to promote transparency and contribute to reproducibility and standardization within the field. In several weeks, NIH will release a special Request for Information asking the research community for their input on the best course of action for the RMIC. Dr. Patterson and the RMIP team welcome the NIDCR Council's feedback.

Stem Cell Identities & Functional Characterization

Dr. Pamela Robey, Senior Investigator, Skeletal Biology Section, DIR, gave a presentation on skeletal stem cells (SSCs) and bone marrow stromal cells (BMSCs). She acknowledged and thanked Drs. Alexander Friedenstein, Maureen Owen, and Paolo Bianco for their pioneering work in the field, as well as members of her team and collaborators. She began her presentation by describing some of the defining characteristics of SSCs and BMSCs. When bone marrow is plated at a very low density, a colony-forming unit-fibroblast (CFU-F) rapidly adheres to the dish and begins to form a colony composed of BMSCs. The colony can then be characterized to determine the potency of the original CFU-F, one of the defining features of a stem cell. These cells have the ability to make cartilage *in vitro* and recreate a bone/marrow organ composed of bone, blood-supporting stroma and marrow adipocytes of donor origin *in vivo,* indicative of an SSC. Hematopoiesis is of recipient origin, but support of hematopoiesis is a defining characteristic of SSCs and BMSCs. As such, the presence of hematopoietic marrow in a transplant is a surrogate marker for the presence of an SSC. Although only one out of five CFU-Fs is multipotent, the colony forming efficiency (CFE) assay is the closest estimate of the stem cell number to date. Given that only one of five CFU-Fs is multipotent, much effort has gone into trying to define the cell surface character of SSCs. Studies have found that the markers $CD146^+$ and $CD271^+$ may be used in conjunction

with one another to enrich for human SSCs. *In vivo*, $CD146^+$ and $CD271^+$ are expressed by pericytes cells that are recruited by blood vessels during development to provide stability.

Dr. Robey and her team performed RNA sequencing on the $CD146^+/CD271^+$ populations and found three clusters of cells, two of which had pericyte-like characteristics. However, when $CD146^+/CD271^+$ cells were used for *in vivo* transplantation, bone was formed, but no marrow growth was established. When the double positive cells were further sorted for leptin receptor ($LEPR^+$), the triple positive cells were found to support the formation of bone and marrow. This appears to be the cell surface phenotype for human SSCs. One major caveat to this study is that virtually 100% of cells are lost during the processing, which is a problem Dr. Robey and her team are working to solve. Dr. Robey and collaborators used serial transplantations to show that SSCs self-renew, which is another defining characteristic of stem cells.

Dr. Robey and her team hypothesize that because SSCs are so central to bone formation, any genetic mutation or microenvironmental change would result in a skeletal disease. They confirmed this hypothesis for fibrous dysplasia of the bone. The team also found that SSCs and BMSCs are part of the hematopoietic stem cell niche and that mutations in SSCs could also affect hematopoiesis. SSCs and BMSCs could be therapeutic targets in some hematological disorders. Dr. Robey would like to use SSCs and BMSCs for regenerating bone. However, there are very few examples of successful use of stem cells as cell therapies. She and her team have spent considerable effort in optimizing *ex vivo* expansion of SSCs and BMSCs, the type of scaffolding needed, and how to best introduce the cells into patients. In 2008, Dr. Robey was given five years of funding to develop clinical grade BMSCs. She and her team developed a drug master file and three INDs. They developed their system using commercially available tissue culture flasks, cell factories and tubing, and used well-defined cell surface markers to ensure that the cells were not contaminated with other cell types. The *ex vivo* expanded cells were further qualified by successful formation of a bone/marrow organ *in vivo*.

Dr. Robey described the Biomedical Excellence for Safer Transfusion (BEST) Study. In this study, researchers performed transcriptome analysis on clinical-grade cell products from eight centers. Some centers clustered closely together, while others were more disparate. *In vivo* transplantation showed a great deal of variability from one center to another. During this study, the team tried to develop a signature for what the bone-forming SSCs/BMSCs were producing. Cell identity and potency are important factors to consider when developing clinical grade products. SSCs/BMSCs' paracrine, immunosuppressive, and immunomodulatory effects for bone reconstruction are less clear and require further study

The Council asked how Dr. Robey imagines treatment delivery for SSC/BMSCs. She responded that the current goal is to understand what controls their fate and what factors cause

them to go into different phenotypes. She invited Council members to contact her at Pamela.robey@nih.gov with any other questions.

Human Skeletal Stem Cells

Dr. Michael Longaker, Deane P. and Louise Mitchell Professor, Vice Chair, Department of Surgery, Co-Director, Institute for Stem Cell Biology and Regenerative Medicine, and Director, Hagey Laboratory for Pediatric Regenerative Medicine at Stanford University, gave the final presentation. He focused his presentation on his lab's research in skeletal stem cell biology, specifically identification of the human skeletal stem cell. He began by reviewing his work in mouse skeletal stem cell biology. In 2015, the Longaker Laboratory published a paper titled "Identification and specification of the mouse skeletal stem cell" (Chan, et al., *Cell*). This led to additional publications identifying an injury-induced skeletal progenitor during fracture healing (Marecic et al., *PNAS*, 2015) and pharmacologic rescue of deficient skeletal repair in diabetic animals by manipulating the niche (Tevlin et al., *Science Translational Medicine*, 2017). Dr. Longaker recognized and thanked Owen Marecic and Drs. Ruth Tevlin and other members of his team for their work on these projects. Finally, in 2018, his laboratory, in collaboration with Dr. Howard Chang's laboratory published a manuscript entitled "Mechanosensitive stem cells acquire neural crest fate in jaw regeneration" (Ransom, Carter, et al., *Nature,* 2018). Dr. Longaker recognized the work of Chase Ransom, Ava Carter and Howard Chang for making this paper a possibility. The data in this paper are remarkable and quite surprising. The ability of the mouse skeletal stem cell (mSSC) to revert back to a neural crest state only under mechanical forces (as a result of distraction osteogenesis) is highly unusual in the adult mouse.

Dr. Longaker went on to tell the story of how his laboratory discovered the human skeletal stem cell in a manuscript entitled "Identification of the human skeletal stem cell" (Chan et al., *Cell* 2018). Dr. Longaker acknowledged the important contributions of Charles Chan, Ph.D., who was first author on both the mouse and human skeletal stem cell papers. This project was challenging because the techniques utilized to discover the mouse skeletal stem cell, such as a rainbow transgenic mouse, were not available in humans. However, the information and techniques used in the mouse paper ultimately led to identifying the human skeletal stem cell (hSSC) from human fetal growth plates.

Podoplanin (PDPN), CD146, CD164, and CD73 were all found to be surface markers of hSSCs. Importantly, none of these markers identify the mouse skeletal stem cell. The hSSCs have characteristics of self-renewal, multipotency, and a skeletal lineage tree hierarchy. The Longaker Laboratory explored whether hSSCs become adipogenic but did not find evidence of adipocyte differentiation in hSSCs. Additional data showed that hematopoietic stem cells could be cultured in *in vitro* for two weeks in serum-free conditions by co-culturing them with the stromal population of hSSCs. These data open the possibility of manipulating hSSCs and having a transplantable niche. Furthermore, the Longaker Laboratory isolated hSSCs from adult bone (discarded hip and knee replacement specimens), induced pluripotent stem cells (iPSC), and adipose tissue. Not surprisingly, at a single cell level, there is heterogeneity within the hSSCs derived from various sources- for example, fetal bone-derived

hSSCs are most similar to iPSC-derived hSSCs, and adult bone-derived hSSCs are most similar to adipose-derived hSSCs. The most heterogeneous population is the adult bone-derived hSSCs.

Given that the Longaker Laboratory isolated both mSSCs and hSSCs, they were able to do a unique set of comparison experiments. For example, colonies derived from hSSCs are one hundred times larger than colonies derived from mSSCs. In addition, mouse fetal bones grown *in vivo* in immunodeficient mice grew significantly less than similar-sized human fetal bones. These data suggest an intrinsic difference between the mouse and human SSCs in terms of growth potential. Dr. Longaker went on to identify genes that were under-expressed in mSSCs compared to hSSCs. The hypothesis was that if he overexpressed those genes in mSSCs, would they generate larger pieces of bone? Of the choices, his laboratory focused on members of the Wnt pathway, and particularly inhibitors DNAJB6 and SOST. Overexpression of the human orthologs of DNAJB6 and SOST in SSCs resulted in significantly larger bone pieces when transplanted into immunodeficient mice. These data, as well as other data in their extensive mouse versus human single cell analyses, can begin to explain why human and mouse skeletons have diverged in size, thickness, etc.

The Council asked to what extent SSCs will know what to do when transplanted in different areas to serve different purposes. Dr. Longaker responded that researchers are still trying to fully understand this. However, SSCs will take on the properties in the niche that they are transplanted in. The Council asked if and how scaffolds are being addressed. Dr. Longaker responded that the scaffolds are currently not as sophisticated as they could be, but the cells are dominant. Dr. Robey responded that she has come across a few scaffolds that work well, including hydroxyapatite and calcium phosphate. HSSCs prefer hard substrates, but weight bearing is an issue. She and her team have found a promising scaffold for cartilage formation and are planning to develop it further. The Council raised the point that BMPs are expensive and difficult to regulate, and asked Dr. Longaker if he has considered pursuing autotherapies instead. Dr. Longaker responded that BMPs are appealing because they open up the possibility of taking a "vending machine" approach to bone replacement and transplants: instead of needing to farm bone out of another part of a patient's body, BMPs allow one to use readily available fat tissue to form bone. The Council asked if bone formed from fat tissue is as durable as other bone. Dr. Longaker responded that six-month studies have shown bone formed from fat tissue and BMP to be durable in the skull.

VII. ADJOURNMENT OF OPEN SESSION

The open session of the NADCRC meeting adjourned at 11:43 am.

CLOSED SESSION

This portion of the meeting was closed to the public in accordance with the determination that it was concerned with matters exempt from mandatory disclosure under Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S. Code and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

IX. REVIEW OF APPLICATIONS

Grant Review

The Council considered 409 applications requesting $161,913,654 in total costs. The Council recommended 244 applications for a total cost of $111,869,193.

X. ADJOURNMENT

The meeting was adjourned at 2:20 p.m. on January 23, 2019

CERTIFICATION

I hereby certify that the foregoing minutes are accurate and complete.

Martha J. Somerman -S

Digitally signed by Martha J. Somerman -S
Date: 2019.04.05 10:30:47 -04'00'

Dr. Martha J. Somerman
Chairperson
National Advisory Dental and Craniofacial Research Council

Dr. Alicia Dombroski
Executive Secretary
National Advisory Dental and Craniofacial Research Council